Steinberg and Durell (1968) revisited: Increased rates of First Episode Psychosis following military induction in Greek Army Recruits.

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Introduction

The influential report by Steinberg and Durell, published as early as 1968 (Steinberg & Durell. 1968), consolidated what was considered until then a mere speculation: exposure to psychosocial stressful life events, such as military enlistment, is sufficient to increase the risk of developing a psychotic disorder in individuals with higher than average pre-existing liability. The authors found that the rate of hospitalization during the first months of military service was significantly higher than during the second year. In the first month, the rate of hospitalization was six times higher than that in the second year. The authors considered that the increased rate of first hospitalization in the early months of military service may be the result of previously undetected chronic psychotic illness. The case records from two patient samples were reviewed and the results indicated that the early detection of individuals with chronic psychotic illness accounted for only a small proportion of the differential rate and that the findings therefore represented a genuine increase in the incidence of acute psychotic symptoms during the early months of service induction (Steinberg & Durell. 1968).

Military service entails a significant level of stress due to family detachment, compulsory coexistence with unknown individuals, contact with weapons, military hierarchy, training and a range of 'initiation rituals' that can add to the psychological pressure. In terms of social interaction and activation of coping strategies to a demanding environment, joining the army could be considered as an objective stressful, adverse event. Adult life events and their upcoming stress adjustment have been linked with psychosis and act cumulatively to previous sensitization resulting from daily stressors (Myin-Germeys *et al.* 2003). Exposure (as a major event in an individual's life) and sensitivity (impaired tolerance to normal stress or increased sensitivity to daily stressors) may predispose an individual to psychotic symptoms. The stress-diathesis model of psychosis suggests that stress acts upon an underlying vulnerability and triggers or exaggerates psychotic symptoms (Walker & Diforio. 1997).

Vulnerability may be shaped by the interplay of environmental factors, such as cannabis use (Large *et al.* 2011), low socio-economic status (Agerbo *et al.* 2015), urbanicity (Vassos *et al.* 2012) and genetic predisposition, making someone more prone to the later development of psychosis (Van Os *et al*. 2008). Moreover, psychosis proneness seems to be related with impaired stress tolerance, indicating that a lower threshold to stress is a core feature of the psychosis risk state (DeVylder *et al.* 2013). The relationship between adjustment to military service and onset of psychosis has been previously studied focusing mainly on epidemiological parameters (Herrell *et al.* 2006 ; Lewis *et al.* 2000). Few studies have examined military service as an objective condition of stress exposure in relation to genetic liability and psychosis onset (Stefanis *et al.* 2007). Studies have established a link between the emergence of neurotic symptoms and anxiety disorders in the context of military service (Hageman *et al.* 2008). The specific stress associated with psychosocial adaptation has been linked to onset of psychotic states in the very first months of military service (Steinberg & Durell. 1968; Hatzitaskos *et al.* 1997). Combat experience, however, may not increase the risk of a psychotic disorder (Reijnen *et al.* 2015). Military duty adjustment implies a psychological strain more similar to the psychosocial stressors that are thought to impact neurotic and psychotic risk in civilian life, while exposure to battle may more specifically impact risk for trauma-related disorders.

The aim of the current study was to identify the timing of FEP onset within military service in Greek army recruits, conform the original study by Steinberg and Durell, who reported higher FEP rates within the first months of service. In addition, we co-examined known risk factors such as cannabis use, socio-economic status and urban environment. Military service in Greece is obligatory for males over 18 years old, however individuals can be enlisted after completing their studies. Therefore, the study age window reflects the critical period (i.e. 18-25 years of age) of FEP peak onset in males.

Methods

Data Selection and Extraction

The data were selected from a total of 451 registered medical files of conscripts diagnosed with psychotic disorder, who were hospitalized in the psychiatric clinic of the Athens Military Hospital, during the years 2005 to 2014. Information for each case was extracted from the records of patients who had diagnosis of psychotic disorder at the end of their hospitalization. During the file screening procedure, two psychiatrists (SD and TM) jointly determined inclusion of each FEP case as appropriate for the study. Those with a previous history of a psychotic disorder and FEP patients that had not been on mandatory service (i.e. military officers or voluntary soldiers) were excluded (n=251). The exact month of hospitalization was unknown for 14 individuals, thus the final sample consisted of 186 male conscripts.

According to standard procedures, all recruits provide a medical history at enlistment and are given a medical screening, which includes a short, unstructured psychological evaluation by a trained army psychologist. No standardised scales or established psychometric tools are used during this procedure. In a second phase, conscripts estimated to have significant psychopathology or aberrant behaviour, undergo clinical evaluation by a military psychiatrist. Recruits who report a positive history of psychotic symptoms or schizophrenia spectrum disorder are usually released from any military obligation. Those with overt mental symptoms, including psychosis, current drug misuse or cannabis use are not allowed to enlist. Finally, recruits with previous duty exemption due to psychological reasons, undergo a thorough psychiatric assessment before joining the army corps. As the study is based on case notes, requiring a method of objective data extraction, a consensus was performed by two psychiatrists (SD and TM), after reviewing all the available information. In the case of disagreement between raters and not enough information to further clarify the issue, the value was left missing.

Outcomes and Exposures

Predetermined variables of interest, which were targeted for extraction from the medical notes, included: a) demographics: i.e. age, education, socioeconomic status, place of birth and residence b) service-related variables i.e. month of hospitalization, service near place of interest, c) potential environmental exposures, i.e. cannabis. For all individuals included in the study, we collected data regarding financial status (defined as high, medium or low as decided by consensus, based on family household income derived from parents' work status), education (defined by highest achieved academic degree), place of birth and residence (defined as capital cities with >1.000.000 population, large cities with <1.000.000 and >100.000 population and small towns or villages with <100.000 population), family record for psychotic disorder (defined as positive for any first and/or second-degree relative, as reported by the patient), history of drug use (regular use was scored if the patient reported daily use or using often over a period of time, while sporadic use was noted if the patient mentioned using a few times lifetime) and type of drug use (defined as "only cannabis", if any history of cannabis use was reported and "multiple substances", if history of other drug use additional to cannabis was reported). The focus of the record search was the time of hospitalization and when the psychotic episode first developed (i.e. month of service). Moreover, the place where FEP developed, i.e. boot camp or other camp near the country borders, and its relation to place of interest (i.e. near family or homeland) was also considered, since physical proximity or distance from family environment during military service may moderate stress resilience. Finally, Duration of Untreated Psychosis (DUP) was defined by either reported onset of positive psychotic symptomatology or overt behavioural change or first noticeable functional decline until the first initiation of antipsychotic treatment. FEP was extracted from the case notes and determined in a consensus procedure. This definition is consistent with the procedure described by Compton et al (Compton *et al*. 2007).

Statistical Analysis

Parametric and non-parametric tests were used as appropriate, depending on the normality of continuous data. Pearson's chi-square test was used to test for association between categorical data. Logistic regression was used to estimate the odds of having the illness onset in the first month versus the other months. All analyses were conducted using SPSS.

Results

FEP onset at first month versus later months

The distribution of FEP cases per month is presented in Fig. 1 and separately for those whose DUP preceded the start of military service, those whose DUP was within the military service and the persons with unknown DUP. Illness onset was unevenly distributed across the 12 months (chi-square=408.9, df=10, $p<0.001$), the proportion with illness in the first month being 50.5%, with additionally slightly elevated proportions across months 2-4. The risk of occurrence in the first month was at least 4.5 times higher than occurrence in any other month.

Month of illness onset and psychosocial factors

The next part of the analysis examined if there were factors affecting the timing of illness onset comparing onset in the first month of the military service to onset in any of the other months. To this end, a binary variable was created (hereafter: first month onset, 1: Yes, 0: No) in order to estimate the odds of a first-month-onset versus the odds of an onset during the remaining months, in relation to several factors. The results are presented in Table 2 in the form of odds ratios (OR). The individuals who originated from small towns/villages had a first-month-onset three times more often than those from medium sized cities. According to the Greek Army Directorate of Research and Informatics, there were differences with respect to

the place of birth between our sample proportions (large cities: 43.2%, medium town: 17.6%, small town 31.8%) and the population (large cities: 35.5%, medium town: 11.6%, small town 52.9%) proportions, whereas as population we considered the total number of conscripts (n= 466510) that were enlisted between the years 2005-2014. To adjust for the under-representation of the small cities we assigned weights and repeated the analysis. The estimated odds of FEP with respect to the place of birth in the weighted sample were similar to the unweighted one [medium vs small towns OR=0.3, 95% CI: (0.1-0.8), p=0.018], while there was no noticeable difference in the odds with respect to the place of residence. Individuals who were serving far away from home had first month illness onset 3.7 times more often than those serving close to place of interest. When both significant predictors were entered simultaneously in the model, the effects remained relatively stable for birthplace (medium vs small towns OR=0.25, 95% CI: 0.1-0.6) and proximity of place of service to home (far from home vs close to home OR=4.9, 95% CI: 1.3-1.8). Among the individuals who reported history of substance use, those who use multiple substances were 4.6 times (more likely to have onset on the first month, compared to those who reported only cannabis use. Due to the relatively small number of individuals reporting substance abuse, a logistic model controlling for place of birth was not applicable. There was no association with family history.

Table 1 here

Duration of Untreated Psychosis

In order to determine when psychosis first developed, data on DUP were also considered. Identifying cases with DUP within the period of military service is critical, as it reflects the emergence of positive symptomatology/aberrant behaviour within the period of military service. DUP was not known for 37 out of 186 patients, while 10 individuals had DUP extending

beyond the point of service initiation (5.4%); these were excluded from analysis. As only 10 individuals had symptom onset outside the period of military service, low power precludes analysis of significant differences between the three groups (DUP before/during military service and DUP unknown). The two groups (known and unknown DUP) were almost identical in all characteristics measured in the study with no large or significant differences across the different relevant variables (*age*: t=0.043, df=179, p=.966, *place of residence*: χ^2=2.602, df=2,p=.272, *birth place*: χ^2=1.834, df=2,p=.400, *marital status*: χ^2=1.137, df=1, p=.286, e*ducation*: χ^2=.527, df=2,p=.768, *financial status*: χ^2=4.155, df=2,p=.125, *postponed service*: χ^2=0.108, df=1, p=.742, *volunteer*: χ^2=1.054, df=1, p=.305, *family history*: χ^2=0.173, df=1, p=.678, *substance use*: χ^2=0.418, df=1, p=.518). It is therefore reasonable to assume that the expected number of individuals with DUP prior to military service should not exceed 5.4%, i.e. n=2 individuals out of 37. As this proportion could not affect the results, the 37 individuals with unknown DUP were included in the analyses in order to ensure no loss of information and power. In case of DUP missing data, the value was set to missing. All analyses were conducted in the final sample of 176 FEP patients for whom the onset of the illness was determined within the period of military service.

Results of DUP analysis are shown in table 2. DUP was known for 149 individuals, while 10 had DUP prior to enlistment, indicating that 139 developed psychotic symptomatology whilst serving. The median DUP of those getting a diagnosis in the first month was shorter than the ones who got the diagnosis later during the service period (either in the complete sample of 149 individuals or only within those who had onset of symptoms within military service, n=139). Retrospective estimation of DUP was found high for 10 patients, who had been psychotic before enlistment for many years and had not received any treatment.

Table 2 here

Discussion

In this study, we attempted a direct replication of the original report by Steinberg and Durell, examining the distribution of hospitalization across the period of military service in all conscripts with FEP. In addition, we examined factors impacting the timing of onset. We hypothesized, based on the original report, that a) most of the conscripts would be hospitalized within the first month and b) most of these onsets would be new, that is most conscripts would not be overtly ill before entering the army. Our findings suggest that the majority of those developing a psychotic illness did so in the first month – and much less in the 11 months thereafter (maximum service period is 12 months). We speculate that psychosocial stress associated with military induction may not only precipitate psychosis in vulnerable individuals, but more specifically can bring forward the onset of positive psychotic symptoms/aberrant behaviour in individuals with a recent negative screening for active psychopathology. Although we cannot exclude the fact that individuals with subtle prodromal symptoms were not detected as such during the medical examination screening procedure, and therefore cannot claim our findings reflect true de novo onset of psychosis, the skewed period of psychosis onset in the first month does suggest an effect of 'bringing forward' the florid manifestation of liability to psychosis. Finally, certain factors (such as service away from home, rural environment at the time of birth, multiple substance use) may hasten FEP onset during military service.

Higher FEP Rate in the first month of service

Results indicate that stress exposure due to military life adjustment favours an earlier FEP onset. Hospitalisation rate was over 4.5 times higher during the first month of service and this argues for a lower stress threshold among psychosis-prone individuals. Stress sensitivity

has been linked to psychotic processing in FEP patients (Reininghaus *et al.* 2016). Furthermore, studies support that stress tends to subside at lower levels towards the end of the service period (Stefanis *et al.* 2007; Martin *et al*. 2006) and it is therefore logical to assume that the first month of military service entails the greatest psychosocial stress, as there is excessive demand for effective social adaptation. So far, the majority of studies focuses on the stress-diathesis hypothesis considering stressors as a homogeneous category, while evidence has shown that the most burdensome stressors concern uncontrollable threats about important goals or social values-related threats (Jones *et al.* 2007). In the framework of military service, which resembles a naturalistic study, the individual struggles to maintain the ‘‘social self’’ against “social defeat” menace under sometimes uncontrollable, social-evaluative situations and this may trigger the development of psychosis. Especially in the first month, when basic training takes place, a ‘rookie’ conscript may experience -in terms of social interaction- devaluation, offences, bullying, isolation and all these to a demanding, alien framework, away from the safe family or social environment. Such sociological adversities may entail a form of tardive traumatisation. Aspects of the military environment during induction may resemble the social defeat conditions that have been linked to increased psychosis risk (Selten *et al.* 2013). Moreover, recent exposure to acute stress or major life events has been linked with imminent onset of psychosis (Wiles *et al.* 2006), while other studies indicate that daily stressors that exceed a person’s coping abilities or a hectic social environmental context, are linked with an increased level of positive psychotic experiences (Tessner *et al.* 2011). The model of clinical staging (McGorry *et al*. 2010) offers an alternative explanation in which distress has reached critical levels and army-related stress is considered a final catalyst for the transition to psychosis.

In order to rule out the possibility that hospitalization during the first month occurred as a result of identifying individuals with a chronic psychotic disorder early in their service attachment, procedures were applied ensuring that medical screening of all military recruits

with a psychiatric history or serious behavioural problems were identified. Information on DUP indicates that the vast majority of patients (139 out of 149) developed psychosis during and not before army enlistment. For this reason, first hospitalization is likely to reflect new onset of positive psychotic symptomatology, reinforcing the hypothesis first proposed by Steinberg and Durell that daily, psychosocial, adaptive stress may induce a psychotic episode. However, we acknowledge the possibility that the unstructured screening procedure for active psychopathology in our population may miss subtle prodromal states (cognitive deficits, negative symptoms) that may partially account for the higher rates of FEP hospitalization observed in the first month of service. Nevertheless, the great majority of those meeting criteria for prodrome will not develop any psychotic disorder – even for those meeting UHR criteria, the rate of non-transition over the next two years is around 90% (Schultze-Lutter *et al*. 2015). Moreover, it is plausible to assume that these FEP cases may be enriched by other than Schizophrenia types of the psychosis spectrum, such as "brief psychotic disorders", and therefore not necessarily associated with a prolonged transition prodromal period. Brief psychotic disorders are deemed to be more sensitive to the deleterious effects of psychosocial stress/environment and a general psychopathology assessment would be unlikely to pick this. Nevertheless, the severe skew with preponderance of onsets in the first months may suggest that the transition from prodromal to florid state of psychosis is similarly brought forward by the stresses of military induction.

Finally, DUP was significantly associated with month of hospitalization, comparing the first month vs the others. DUP was found to be significantly shorter (mean DUP: 8 days for 1st month and 19 days for other months), as an outcome of both psychosocial stress in the army life context and early recognition by medical services. Assuming that detection is stable throughout the army service, the finding of an ultra-short DUP in the first month perhaps indicates that psychosocial stress-induced psychosis has an acute onset or results in more florid psychopathology, facilitating detection.

Psychosocial Stress in the Military Environment and Environmental Risk Factors for Psychosis

Few factors were investigated in order to determine pre-existing lifetime social stress exposure. Factors, such as trauma, attachment difficulties, urbanicity and cannabis use, have been established as environmental risk factors for psychosis (Van Os *et al.* 2010). In terms of chronic stress or environmental risk, an individual, who is chronically and cumulatively exposed to psychosocial stress, may be at greater risk of developing psychotic symptoms. It has been suggested that stress and psychosis may interact in a pathway of underlying vulnerability, characterized by increased emotional and psychotic reaction to stress, resulting in both transient and persistent psychotic symptoms (van Winkel *et al.* 2008). In our sample, the majority of 1st month FEP patients were serving away from home. This may reflect separation difficulties or low adjustment abilities, when away from family, friends and daily routine. Another explanation is that all conscripts spend the first month of their service period in boot camps, that are usually far from their home and thus adjustment demands are higher. Urbanicity and rural environment appear less protective for earlier FEP onset in our sample, in contrast to evidence of a dose-response relationship between urbanicity and psychosis emergence (Vassos *et al.* 2012). Likewise, history of multiple drug use may make individuals more vulnerable to earlier first time appearance of psychotic symptomatology combined with army adaptation stress, rather than cannabis use per se, as could have been expected (Large *et al.* 2011). It is doubtful whether previous use indicates lower stress threshold (and thus usage serves self-healing purposes) or drug use itself makes people more vulnerable to stress. A family history for psychosis or schizophrenia was not associated with earlier FEP onset, which is not in agreement with evidence suggesting that increased stress-sensitivity is associated with higher familial psychosis risk (Myin-Germeys *et al.* 2001). From another point of view, a recent study by Shakoor et al. (Shakoor *et al*. 2016) suggests that stressful life

events, as an environmental risk factor for psychosis, can be viewed within the context of genetics, indicating that there may be a shared genetic propensity between stressful life events and psychotic experiences.

Limitations

Several methodological issues should be addressed, since this study is retrospective, based on medical file notes. Consensus between psychiatrists does not ensure validity, since no psychometric tools were used for data extraction. DUP is a proxy construct with ambiguous validity and thus determining the exact psychotic onset is difficult. In this sample, DUP measurement was not based on an established psychometric tool. Due to lack of information, we were unable to focus on the prodromal phase, by controlling for negative or cognitive symptoms preceding positive psychotic symptomatology. Moreover, important factors, such as premorbid adjustment and developmental adversities, that determine pre-existing life stress and can be considered as important moderators, were not analysed. It should be also acknowledged that there is a potential reporting bias when asking people for drug use and a family history of psychosis. Finally, in terms of defining the psychotic episode, no data on course and outcome was available. Therefore, while onset is increased early in the period of army induction, no conclusions can be drawn regarding outcome beyond the first psychotic episode.

Implications

In conclusion, we found that there is an excess of FEP cases in the first month of military service**.** Beyond the stress-diathesis model, which states that psychotic symptoms may emerge, whenever a threshold of stressors exceeds an individual's vulnerability level and coping resources, we speculate that psychosocial stress associated with compulsory military induction may not only precipitate but rapidly bring forward positive psychotic

symptomatology/aberrant behaviour in apparently healthy individuals, with a prior negative screening for active psychosis and symptom onset within days of enlisting for military service. We cannot exclude that some false-negative prodromes were counted as FEP cases although this does not preclude a hypothesised effect of military induction on bringing forward the transition from prodrome to florid first psychotic episode. The findings support the hypothesis that psychosocial stress induces positive psychotic symptoms, with hospitalization as final outcome. We do not postulate that military service causes psychotic symptomatology in individuals, that would otherwise not have developed, but as indicated before, psychosocial stress may be a fire wick to a pre-existing covert genetic and/or environmental liability. Our findings for lower stress threshold and early FEP onset (under existing adverse effects) differentiate from the insidious development of psychotic symptomatology as met in other patients. Ultra-short DUP is another feature indicating that psychosocial stress combined with the lack of coping abilities and obligatory stay in camp, may lead to rapid psychotic blow and/or floridness of symptoms that can be easily and quickly detected. Our analysis revealed that there could be risk factors (such as service away from home, multiple substance vs only cannabis use, low urban environment at the time of birth) for early FEP onset.

Further implications of our findings concern early and in-time recognition of such high-risk populations. It is suggested that psychosocial stress and the demand for social adaptation could be a key mediator to earlier and acute psychosis onset, while underlying neurobiological pathways that hasten this progress should be further examined. Finally, the time of emergence, as a strong indicator for low stress-resilience, implies that early psychosis recognition by identifying stress prone individuals and intervention by encouraging stress control methods in such demanding environments, should be at the focus of clinical attention.

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Declaration of interest

None.

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463 Table 1: Odds-ratios for First Month vs Later Month Psychosis Onset

First month onset:	No N (%)	Yes N (%)	OR (95% CI)	Wald test
Birth place				
Large (capital) cities[1]	40 (52.6)	36 (47.4)	0.6 (0.3, 1.3)	p=0.190
Medium town[2]	22 (71)	9 (29)	0.3 (0.1, 0.7)	**p=0.009**
Small town[3]	23 (41.1)	33 (58.9)	*reference category*	
Place of residence				
Large (capital) cities[1]	44 (52.4)	40 (47.6)	0.7 (0.3, 1.4)	p=0.29
Medium town[2]	19 (65.5)	10 (34.5)	0.4 (0.2, 1.0)	p=0.056
Small town[3]	21 (42.9)	28 (57.1)	*reference category*	
Education level				
Compulsory (9 years)	16 (50)	16 (50)	1.5 (0.6, 3.6)	p=0.374
Secondary (12 years)	34 (47.2)	38 (52.8)	1.7 (0.8, 3.5)	p=0.166
Higher (14 or more years)	30 (60)	20 (40)	*reference category*	
Financial status				
Low	11 (35.5)	20 (64.5)	1.1 (0.5, 2.4)	p=0.748
Medium	40 (54.1)	34 (45.9)	0.9 (0.2, 6.3)	p=0.070
High	24 (57.1)	18 (42.9)	*reference category*	
Proximity of Service				
Service far from hometown	73 (48)	79 (52)	3.7 (1.2, 11.7)	**p=0.028**
Service close to hometown	13 (76.5)	4 (23.5)	*reference category*	
Family history (any 1st or 2nd degree relative)				
Yes	29 (54.7)	24 (45.3)	1.3 (0.7, 2.5)	p=0.465
No	49 (48.5)	52 (51.5)	*reference category*	
Drug Use				
No	61 (52.6)	55 (47.4)	1.2 (0.6, 2.3)	p=0.672
Yes	24 (49)	25 (51)	*reference category*	
Frequency of Drug Use				
Regular	6 (35.3)	11 (64.7)	2.5 (0.7, 8.8)	p=0.155
Occasional	15 (57.7)	11 (42.3)	*reference category*	
Type of Drug Use				
Multiple substances	3 (23.1)	10 (76.9)	4.6 (1.1, 20.1)	**p=0.042**
Only Cannabis	18 (58.1)	13 (41.9)	*reference category*	

464 [1]>1,000,000 residents, [2]>100,000 residents, [3]<100,000 residents

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466 *Table 2: DUP analysis on complete and symptom onset within service sample*

		Complete sample (n=149)		Symptom onset within service (n=139)	
		First month diagnosis		First month diagnosis	
		No	Yes	No	Yes
Duration Of Untreated Psychosis (days)	Median	10	5	10	5
	Minimum	1	1	1	1
	Maximum	550	1460	90	30
	Mean	37	79	19	8
	Std. Dev.	91	273	22	7
Comparison	Mann-Whitney	U= 2026, **p=0.005**		U= 1477.5**, p<0.001**	

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